Complete Summary

GUIDELINE TITLE

Pharmacologic treatment of acute major depression and dysthymia.

BIBLIOGRAPHIC SOURCE(S)

Pharmacologic treatment of acute major depression and dysthymia. Ann Intern Med 2000 May 2;132(9):738-42. [7 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Major depression and dysthymia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Psychiatry

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To answer the following questions:

1. What is the evidence supporting the benefits of pharmacologic treatment?
2. What are the data on the efficacy and side effect profiles of "newer" compared with "older" pharmacotherapies?
3. How can the evidence assist physicians and patients in making informed decisions about treatment options?

TARGET POPULATION

Adults and elderly patients with acute major depression or dysthymia and with no co-morbid conditions.

INTERVENTIONS AND PRACTICES CONSIDERED

Antidepressants, including:

1. "Older" agents, such as the first- and second-generation tricyclic antidepressants, heterocyclics, and monoamine oxidase inhibitors;
2. More well-known "newer" classes of antidepressants, such as selective serotonin reuptake inhibitors;
3. Lesser-known new agents, such as serotonin and noradrenaline reuptake inhibitors; selective norepinephrine reuptake inhibitors; reversible inhibitors of monoamine oxidase; 5-hydroxy-tryptophan$_2$(5-HT$_2$) receptor antagonists; 5-HT$_{1a}$ receptor agonists; gamma-aminobutyric acid mimetic agents; dopamine reuptake inhibitors; dopamine antagonists; and
4. Herbal remedies, such as hypericum (St. John's wort).

MAJOR OUTCOMES CONSIDERED

Primary Outcomes

- Symptomatic response rate to antidepressant treatment
- Total discontinuation rates (dropouts), and rates of discontinuation because of adverse events.

Note: Clinical improvement was defined as 50% or greater improvement in score on the Hamilton Rating Scale for Depression or Montgomery Asberg Depression Rating Scale or "much to very improved" on the Clinical Global Impression Scale.

Secondary Outcomes

- Health-related quality of life
- Functional status
- Suicide

Note: these outcomes were reported too infrequently for analysis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

English-language and non-English-language literature was identified by using the Cochrane Collaboration Depression, Anxiety and Neurosis Group's specialized registry of 8451 clinical trial articles and from references of pertinent meta-analyses and consultation with experts. The specialized registry contained trials addressing depression identified from multiple sources, including electronic databases, such as MEDLINE, EMBASE, PsychLIT, LILACS, Psyndex, SIGLE, CINAHL, Biological Abstracts, and The Cochrane Library; hand searches of 69 psychiatry-related journals; and contacts with 30 pharmaceutical companies.

Sources were searched from 1980 to January 1998 to capture literature relevant to newly released antidepressants. The terms depression, depressive disorder, or dysthymic disorder were combined with a list of 32 specific "newer" antidepressants and herbal treatments to yield 1277 relevant records. The newer antidepressants are selective serotonin reuptake inhibitors; serotonin and noradrenaline reuptake inhibitors; selective norepinephrine reuptake inhibitors; reversible inhibitors of monoamine oxidase; 5-hydroxy-tryptophan (5-HT2) receptor antagonists; 5-HT_{1a} receptor agonists; gamma-aminobutyric acid mimetics; dopamine reuptake inhibitors and antagonists; and herbal remedies, such as hypericum. Randomized, controlled trials that were at least 6 weeks in duration; compared a newer antidepressant with another antidepressant (newer or older), placebo, or psychosocial intervention; involved participants with depressive disorders; and had a clinical outcome were reviewed. Two or more independent reviewers identified 315 such trials.

NUMBER OF SOURCE DOCUMENTS

1277 identified from the searches; 315 articles met the inclusion criteria for review

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Two persons independently abstracted data from 315 selected clinical trials. Data were synthesized descriptively, with attention to participant and diagnostic descriptors; study design, including randomization method and blinding; intervention characteristics; and clinical outcomes. When the studies were conceptually homogenous, quantitative analyses were done by using an empirical Bayes random-effects estimator method. Conceptual homogeneity required similar trial design, comparison of similar drug classes, diagnostic homogeneity, and adequate numbers of trials to justify pooling. Statistical heterogeneity was evaluated by using the chi-square test for homogeneity and Galbraith plots to identify outliers. When statistical heterogeneity was identified, outlier studies were reviewed to identify possible reasons for heterogeneity and studies were reanalyzed without the outliers.

Primary outcomes were symptomatic response rate, total discontinuation rates (dropouts), and rates of discontinuation because of adverse events. Secondary outcomes were health-related quality-of-life, functional status, and suicide. Response rates were defined as a 50% or greater improvement in symptoms as assessed by a depression symptoms rating scale or a rating of much or very much improved as assessed by a global assessment method. Response rates were computed by using a modified intention-to-treat approach. This approach computes response rates as the number of patients who stay in treatment and get better divided by the total number of randomly assigned patients. The modified intention-to-treat analysis produces an estimate of treatment effect that is conservative because it assumes that all persons who drop out of the study early receive no benefit. A sensitivity analysis was based on an end point method. In this method, the denominator for the risk ratio was the number of participants who completed follow-up or whose last observation was carried forward.

Funnel plots with the Beggs rank-order correlation test and the Egger regression approach were used to estimate the possibility of publication bias whenever a quantitative meta-analysis was performed.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was approved by the Board of Regents on July 17, 1999.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

1. For primary care patients with acute major depression or dysthymia, including elderly persons without significant comorbid conditions, physicians should consider either tricyclic antidepressants or newer antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), as equally efficacious treatments. For short-term treatment of mild acute depression, St. John's wort may be considered, but patients should be cautioned that this treatment is not approved by the U.S. Food and Drug Administration and that preparations may vary substantially from those tested in randomized trials.
2. Because older and newer antidepressants are equally efficacious, the physician and patient should jointly review the adverse effect profiles of both drug classes so that an agent that fits the clinical needs of the patient can be chosen.
3. Antidepressant medication should be continued at the same dose for at least 4 months beyond initial recovery or improvement to decrease the probability of short-term relapse. If at 6 weeks a patient shows no response or a poor response to an adequate dose of antidepressant medication, treatment should be changed.
4. Physicians should ensure that every instance of a serious adverse effect is accurately reported to the U.S. Food and Drug Administration in a timely manner, either through their Web site at www.fda.gov/medwatch/report/hcp.htm, by telephone at 800-FDA-1088, or by fax at 800-FDA-0178.

CLINICAL ALGORITHM(S)

The following algorithm is available from the American College of Physicians (ACP) Web site:

- Pharmacological Treatment of Depression.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Guidelines are based on evidence gathered by the San Antonio Evidence-based Practice Center from 315 eligible randomized controlled trials that evaluated pharmacotherapies for depression.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Is Pharmacologic Treatment of Depression Beneficial?

The Evidence-based Practice Center report found evidence that valid conclusions could be drawn about the comparative efficacy of selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, reversible inhibitors of monoamine oxidase, 5-hydroxy-tryptophan$_2$ receptor antagonists, and St. John's wort. Compared with placebo, treatment with these classes of drugs resulted in clinically and statistically significant improvement of acute major depression. In primary care settings, the average treatment response difference was 25%, and in elderly persons without comorbid conditions, the difference was 20%. The combined average treatment response difference was approximately 20%. In addition, for treating dysthymia, the effect difference of selective serotonin reuptake inhibitors compared with that of placebo (59% and 37%) was clinically and statistically significant.

Are Newer Drugs or Herbs Better Than Older Drugs in Treating Depression?

No clinically or statistically significant differences in efficacy were found within selective serotonin reuptake inhibitors or between selective serotonin reuptake inhibitors and tricyclic antidepressants for treatment of major depression. However, for treating dysthymia, sufficient evidence was available for evaluation of only two selective serotonin reuptake inhibitors - fluoxetine and sertraline - and for ritanserin, a 5-hydroxy-tryptophan$_2$ receptor antagonist that is not available in the United States. St. John's wort has been shown to be more efficacious than placebo; whether it is as efficacious as tricyclic antidepressants given in adequate doses has not been established. Dosages of tricyclic antidepressants may have been subtherapeutic, and statistical evidence indicated publication bias in the St. John's wort studies.

POTENTIAL HARMS

Side Effect Profiles and Patient Preferences

Dropout rates. In clinical trials, overall dropout rates did not differ significantly between active treatments. The rate of dropout due to adverse effects was slightly higher (and statistically significant) for first-generation tricyclic antidepressants than for selective serotonin reuptake inhibitors (16% compared with 11%; difference, 5 percentage points [95% CI, 2 to 6 percentage points]). No differences in adverse effect-related dropout rates were found between second-generation tricyclic antidepressants and selective serotonin reuptake inhibitors. Only 1.5 percent of persons taking St. John's wort discontinued use because of adverse effects, which were not well described.

Common adverse effects of antidepressants:

- The 11 most common adverse effects of selective serotonin reuptake inhibitors and tricyclic antidepressants are: anxiety, blurred vision, constipation, diarrhea, dizziness, dry mouth, headache, insomnia, nausea, tremors, and urinary disturbance.
- Adverse effects that were significantly more common with selective serotonin reuptake inhibitors than with tricyclic antidepressants were diarrhea (12% and 3%), headache (15% and 11%), insomnia (13% and 6%), and nausea (19% and 9%). Adverse effects that were significantly more common for tricyclic antidepressants than for selective serotonin reuptake inhibitors were blurred vision (10% and 6%), constipation (21% and 8%), dizziness (19% and 8%), dry mouth (48% and 18%), tremors (11% and 7%), and urinary disturbance (8% and 3%).
- Evidence indicates that some adaptation to nausea and dizziness occurs after 4 to 6 weeks of treatment with selective serotonin reuptake inhibitors.
- In clinical practice, patients report that sedation is also a common side effect of antidepressant drugs, but it was not mentioned in the studies.

Other important side effects of both tricyclic antidepressants and selective serotonin reuptake inhibitors include sexual dysfunction and suicide attempts. Fewer than 10% of the trials explicitly reported suicide attempts and suicides. Because of small numbers, these events were not compared. In 11% of the trials, diverse types of sexual dysfunction were reported, including nonspecific sexual symptoms, ejaculatory abnormality, decreased libido, male impotence, erectile dysfunction, and anorgasmia. The data were insufficient to estimate incidence rates, thus making quantitative comparisons among antidepressants impossible.

Uncommon but serious adverse effects of antidepressants:

- Nine uncommon (<1% occurrence) but serious adverse effects were associated with selective serotonin reuptake inhibitors: bradycardia, bleeding, granulocytopenia, seizures, hyponatremia, hepatotoxicity, the serotonin syndrome, extrapyramidal effects, and mania in unipolar depression.
- Serious adverse effects of tricyclic antidepressants were orthostatic hypotension, the neuroleptic malignant syndrome (similar to the serotonin syndrome), decreased seizure threshold, and cardiac arrhythmias.
- St. John´s wort was not associated with any serious adverse events.
- Discontinuation of selective serotonin reuptake inhibitors, without titrating the dosage downward, may result in withdrawal symptoms, such as delirium, mania, and postural hypotension.

The potential for increased risk for suicide deserves special mention because of its seriousness. Two cohort studies and seven reviews of trials have shown a trend toward lower risk for suicide in patients treated with selective serotonin reuptake inhibitors. This effect is presumably due to treatment of the underlying depression. In the event that depressed patients attempt suicide by drug overdose, the selective serotonin reuptake inhibitors are judged to be relatively less likely than other antidepressants to be lethal. However, overdoses with any of these agents can be fatal.

Because the current rates of reporting adverse events ranges from 1 in 100 to 1 in 4600 incidents, the cumulative effect of nonreporting may lead to

misconceptions about the safety of a pharmaceutical agent, possibly resulting in unnecessary suffering and deaths.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Although the evidence was sufficient to evaluate treatment in adult primary care settings and in elderly patients with no comorbid conditions, it was insufficient to evaluate treatments of other depressive disorders, such as subsyndromal depression and refractory depression. Similarly, evidence was insufficient to evaluate the treatment of depression in adolescents or patients with comorbid psychiatric conditions, and elderly patients with co-morbidities.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Pharmacologic treatment of acute major depression and dysthymia. Ann Intern Med 2000 May 2;132(9):738-42. [7 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000

GUIDELINE DEVELOPER(S)

American College of Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Physicians (ACP)

GUIDELINE COMMITTEE

Clinical Efficacy Assessment Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American College of Physicians (ACP) Web site.

Print copies: Available from the American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106-1572.

AVAILABILITY OF COMPANION DOCUMENTS

The statements made by the American College of Physicians (ACP) in the guideline document were developed using the information provided in the following background paper and evidence report:

- Williams JW, Mulrow CD, Chiquette E, Noël PH, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. Ann Intern Med 2000 May 2;132(9):743-56.

  Electronic copies: Available from the ACP Web Site.

Print copies: Available from ACP, 190 N. Independence Mall West, Philadelphia, PA 19106-1572.

- Mulrow CD, Williams JW Jr, Trivedi M, Chiquette E, Aquilar C, Cornell JE. Treatment of Depression: Newer Pharmacotherapies. Evidence Report/Technology Assessment No. 7. Rockville, MD: Agency for Health Care Policy and Research; February 1999. AHCPR Publication No. 99-E014.

  Electronic copies: Available in summary form from the Agency for Healthcare Research and Quality (AHRQ) Web site; this document is also available in full-text from the National Library of Medicine's Health Services/Technology Assessment Text (HSTAT) Web site.

  Print copies: Available free of charge from the AHRQ Clearinghouse, 1-800-358-9295.

Information contained in these background papers is represented in the methodology fields of the NGC summary (i.e., Methods to Collect Evidence; Methods to Analyze the Evidence; Cost Analysis).

The following are also available:

- An algorithm on the pharmacological treatment of depression. Electronic copies available from the ACP Web site.
- Pharmacotherapies for acute major depression (summary). Electronic copies available from the ACP Web site.

This summary and the algorithm file are also available for download to the handheld computer (PDA/Palm) from the ACP Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on October 26, 2000. The information was verified by the guideline developer on November 7, 2000.

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